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Psychotropic Drugs (2) Interaction Between Monoamine Oxidase (MAO) Inhibitors and Other Substances

by Folke Sjöqvist MD
(The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA and Karolinska Institutet, Stockholm, Sweden)

Abstract
Monoamine oxidase inhibitors (MAOI) in clinical use have an irreversible action on MAO, and this persists until the enzyme has been resynthesized. The effects of small daily doses of MAOI are therefore cumulative. The biochemical effects of these drugs will involve several substrates of MAO, e.g. dopamine, tyramine, serotonin and, to a lesser extent, noradrenaline and adrenaline.

MAO probably regulates the metabolism of catecholamines and serotonin in tissues, while catechol-O-methyltransferase is responsible for the metabolism of circulating noradrenaline and adrenaline.

Certain pharmacological effects of MAOI are related to the accumulation of monoamines in various tissues that follows the decrease of intraneuronal deamination. Among these effects are reversal of the reserpine syndrome in animals and augmentation of the pharmacological action of monoamines. Other effects are unrelated to the inhibition of MAO, e.g. immediate desynchronization of EEG and initial pressor effects.

MAOI may potentiate or change the action of several other drugs and even certain foods. The mechanisms involved are usually reasonably predictable from animal experiments. Substrates of MAO, e.g. dopamine and tyramine, evoke augmented and prolonged effects in patients treated with MAOI. This is partly due to an impaired metabolism of the circulating amines. In addition, inhibition of intestinal and hepatic MAO largely increases the absorption of tyramine from cheeses and other foods. Usually innocuous amounts of tyramine may therefore cause hypertensive reactions in patients treated with MAOI. Indirectly acting sympathomimetic amines, such as amphetamines, ephedrine and MAOI with amphetamine-like properties, can be potentiated, because they may release increased amounts of noradrenaline from sympathetic nerve endings after MAO inhibition. The effects of any amine, whether a substrate of MAO or not, may be enhanced by MAO inhibitors producing postganglionic block. This is due to 'denervation' supersensitivity of adrenergic receptors.

Harmful pharmacological interaction is also possible between MAO inhibitors and agents which release (reserpine) or replete (amine precursors, e.g. L-DOPA in broad beans) monoamines centrally and peripherally. Drugs that sensitize adrenergic and tryptaminergic receptors to the action of monoamines, e.g. imipramine-like compounds, may be greatly potentiated by MAO inhibitors. The antihypertensive effects of thiazides and ganglion-blocking agents may be enhanced by MAOI. A few drugs are known to exert prolonged effects in occasional patients treated with MAOI, e.g. pethidine, phenothiazines and pentobarbital. MAOI may possibly decelerate the metabolism of these compounds by a nonspecific inhibition of liver microsomal enzymes. Finally, a great number of agents have been found empirically to evoke augmented effects after inhibition of MAO, e.g. insulin and anti-Parkinson drugs.

The clinically important antidepressive drugs can be classified as either monoamine oxidase (MAO) inhibitors or iminodibenzyl derivatives (imipramine-like drugs). It is impossible to rank individual drugs according to antidepressive efficacy since few meaningful comparative studies have been made. At the most, the evidence from the somewhat controversial literature suggests that imipramine-like drugs are more effective than MAO inhibitors (Cole 1964, Medical Research Council 1965) and they have, therefore, been recommended as the drugs of choice in the treatment of depression (*Medical Letter* 1964). According to Cole (1964) both drug groups appear to be significantly superior to a placebo, but no more effective than electroconvulsive therapy. A more recent study failed to demon-

strate an antidepressive effect of the MAO inhibitor phenelzine (Medical Research Council 1965). It is questionable whether other drug types have significant antidepressive activity in man.

The MAO inhibitors have fallen into disrepute because they can cause toxic side-effects and hazardous interactions with other drugs, and even certain foods. Iproniazid,[1] the first MAO inhibitor to be used in the treatment of depression, was taken off the American market because of its hepatotoxicity. Pheniprazine was subsequently withdrawn because of its association with hepatitis as well as toxic amblyopia. The toxic effects of MAO inhibitors *per se* have been dealt with at length in earlier reviews (cf. Pletscher *et al.* 1960). However, the potential danger of combining these compounds with other substances has not been emphasized enough until recently (Holmberg & Sjöqvist 1964 *a*, *b*; Goldberg 1964). Most of the reported clinical cases of harmful interaction between MAO inhibitors and other compounds could have been predicted from model experiments in animals. This paper describes the pharmacological basis for some of these interactions.

Pharmacological Survey[2]

As early as 1938, Gaddum & Kwiatkowski pointed out that some drugs might evoke their pharmacological effects by inhibition of catecholamine catabolism. The simultaneous discovery that iproniazid caused euphoria in tuberculous patients (Selikoff *et al.* 1952) and inhibited monoamine oxidase (Zeller *et al.* 1952) initiated intense research on the relationship between MAO-inhibiting and antidepressive effects of various agents.

Monoamine Oxidase

The monoamine oxidases (MAO) can be classified according to substrate and inhibitor specificity (Blaschko *et al.* 1959, Zeller & Fouts 1963). The clinically important MAO occur in mitochondria in most parenchymatous tissues of vertebrates and reach particularly high concentrations in the intestine and liver. MAO deaminates several aliphatic and aromatic amines of biological interest, including dopamine, tyramine, 3-methoxytyramine, tryptamine, 5-hydroxytryptamine (serotonin) and, to a lesser extent, noradrenaline and adrenaline (for details, *see* Erspamer 1961). The biochemical action of MAO inhibitors will, therefore, not be restricted to one particular substrate, but will involve several amines. The relative importance of these biochemical effects is determined by the concentration, biological activity, and turnover rate of the different amines in the various tissues and the occurrence of alternative metabolizing enzymes, e.g. catechol-O-methyltransferase for noradrenaline and adrenaline (see below). Since monoamine stores turn over continuously but the amines are released discontinuously, MAO is necessary to regulate the tissue metabolism of catecholamines and serotonin and thereby indirectly control the concentrations of pharmacologically active amines stored in nerve endings (Spector *et al.* 1960). Catechol-O-methyltransferase, on the other hand, inactivates noradrenaline and adrenaline after their release into the circulation (Kopin & Axelrod 1963).

Classification of MAO Inhibitors

As seen in Table 1, there are four main groups of compounds with MAO-inhibiting properties. The hydrazines and tranylcypromine and pargyline are all potent MAO inhibitors, in clinical use. Amphetamine, ephedrine and cocaine, on the

Table 1
Chemical classification of MAO inhibitors

(1) Hydrazines:	iproniazid (Marsilid) nialamide (Niamid) phenelzine (Nardil) pheniprazine (Catron, Cavodil) isocarboxazid (Marplan) mebanazine (Actomol)
(2) Harmala alkaloids	
(3) Tryptamine derivatives:	etryptamine (Monase) alpha-methyl-tryptamine
(4) Others:	pargyline (Eutonyl) tranylcypromine (Parnate) amphetamine, ephedrine, cocaine

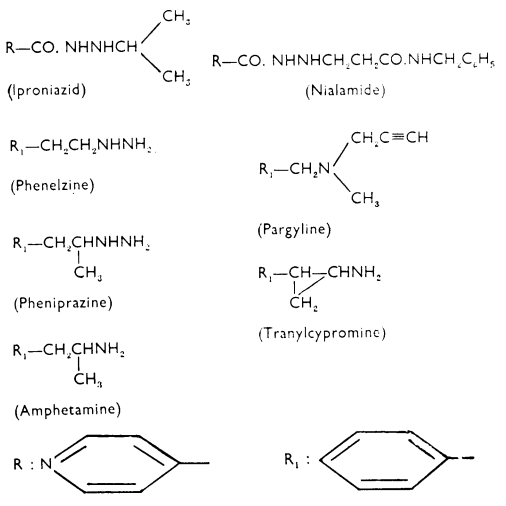

Fig 1 *Structural formulæ of MAO inhibitors in clinical use and amphetamine*

[1]For proprietary names of MAO inhibitors see Table 1

[2]Abbreviations used: NA, noradrenaline. A, adrenaline. DA, dopamine. 5-HT, serotonin. TA tyramine

other hand, are weak MAO inhibitors, even *in vitro*. The structural formulæ of some MAO inhibitors and amphetamine are given in Fig 1. It is particularly important to emphasize the structural similarity between amphetamine, tranylcypromine and, to a lesser extent, pheniprazine and phenelzine. The last three have amphetamine-like properties, which are unrelated to their effect on MAO (see below).

Biochemical Effects of MAO Inhibitors

(1) *Irreversible inhibition of MAO:* The clinically used MAO inhibitors are rapidly metabolized, but the enzyme inhibition is irreversible and thus persists for a long time after the disappearance of the parent compound and its metabolites. Accordingly, MAO activity can be restored only by resynthesis of the enzyme, an extremely slow process. The effect of small daily doses of MAO inhibitors is cumulative (cf. Pletscher *et al.* 1960).

Iproniazid is the prototype of a slowly acting irreversible MAO inhibitor. Pheniprazine acts more rapidly, has a longer duration of action and is equally effective as iproniazid in inhibiting liver MAO; on a molar basis it is fifty times more potent as an inhibitor of brain MAO. MAO inhibitors may thus vary in their relative effects on brain enzymes, compared with their effects on enzymes of the liver, intestine and other peripheral sites. The organ specificity of MAO inhibitors has been studied by Horita & McGrath (1960). The harmala alkaloids are short acting and inhibit the enzyme reversibly.

(2) *Increase of the tissue concentration of free amines:* Monoamines are bound and stored in subcellular particles within monoaminergic[1] nerves, e.g. NA in 'dense cored vesicles' (Richardson 1962), while MAO is localized in mitochondria. Following inhibition of MAO, there is a rapid accumulation of monoamines in these stores due to a decreased intraneuronal deamination (Kopin & Axelrod 1963). The increase of the amine stores has been demonstrated biochemically, histochemically, and by electron microscopy. There is an increase in the concentrations of dopamine, noradrenaline, serotonin and other amines in many organs, especially the brain (cf. Brodie *et al.* 1959, Pletscher *et al.* 1960). Specific histochemical methods reveal that MAO inhibitors increase the content of noradrenaline and serotonin in cell bodies and other parts of central and peripheral (NA alone) monoaminergic neurons (Dahlström & Fuxe 1964, Norberg 1965). MAO inhibitors have also been reported to increase the number of presumed subcellular storage particles of NA in adrenergic nerve terminals in the brain (Pellegrino de Iraldi & De Robertis 1964). The increase in amine concentrations is particularly marked after simultaneous administration of MAO inhibitors and the corresponding amine precursors (Carlsson *et al.* 1957, Udenfriend *et al.* 1957, Everett *et al.* 1959).

The effects of MAO inhibitors on monoamines such as NA and 5-HT are more marked centrally than peripherally. This is probably due to a rapid synthesis of brain amines, and to the brain-blood barrier, which traps the formed and released amines. After very large doses of pargyline, primary catecholamines have been demonstrated histochemically in tissues surrounding adrenergic cell bodies and nerve terminals in the brain (Dahlström & Fuxe 1964). This observation supports the concept that an overspill of released monoamines onto receptors in the brain contributes to the central effects of pargyline and other MAO inhibitors (cf. Spector *et al.* 1963). MAO inhibitors do not cause an appreciable elevation of the endogenous levels of 5-HT and NA in peripheral tissues, although exceptions to this general rule are known (Pletscher 1958, Shore *et al.* 1958).

There are differences in the times of onset and duration of action of various hydrazine and non-hydrazine MAO inhibitors and also important species differences in their effects on various parts of the brain (cf. Pletscher *et al.* 1960, Everett *et al.* 1963). As a rule, about 80% inhibition of MAO is necessary in order to increase the monoamine levels in the brain (Chessin *et al.* 1959).

(3) *Effects on the metabolism of administered and released amines:* It is known that inhibition of MAO prolongs and potentiates the action of tyramine (TA), but not adrenaline and noradrenaline, in animals (Griesemer *et al.* 1953, Burn *et al.* 1954). Axelrod (1957) showed that O-methylation is the major means of metabolic inactivation of injected catecholamines. Horwitz *et al.* (1960) then demonstrated that the pressor effect of dopamine (another substrate of MAO) was markedly augmented and prolonged in patients receiving pheniprazine, nialamide and tranylcypromine. The pressor effects of noradrenaline and methoxamine, which are not metabolized by MAO, were augmented to a lesser degree but were not prolonged. Furthermore, the augmentation occurred only after the development of postural hypotension (cf. Fig 3; see below). Horwitz *et al.* (1964) recently described marked potentiation of the pressor effects of tyramine given orally and intravenously in patients treated with pargyline.

Experiments by Kopin & Axelrod (1963) indicate that MAO plays a minor role in the

[1]Monoaminergic neurons release noradrenaline, dopamine or serotonin at the nerve terminals

initial metabolism of catecholamines released into the circulation from the adrenal medulla or from sympathetic nerve terminals. Moreover, the effect of MAO is dependent upon the origin and mode of depletion of the catecholamine. Thus, MAO is of minor importance for the inactivation of noradrenaline released peripherally by nerve stimulation, ganglionic stimulants, tyramine and amphetamine (Kopin & Axelrod 1963). Tyramine releases the active NA into the circulation, where most of the transmitter is O-methylated. By contrast, the major part of NA released by reserpine is metabolized intraneuronally by MAO and enters the circulation as deaminated inactive metabolites. Following inhibition of MAO, a large proportion of the NA released by reserpine can reach receptor sites in an active form.

Other drugs such as guanethidine, alpha-methyldopa and alpha-methyl-m-tyrosine have both reserpine- and tyramine-like actions. The effects of noradrenaline released by these drugs may, therefore, be potentiated after MAO inhibition (cf. Fig 3, Table 8).

From these model experiments, it is quite clear that substrates of MAO (DA, TA, &c.) and drugs which release amines by a reserpine-like action may evoke untoward pharmacological effects in patients treated with various MAO inhibitors. The possible interactions are summarized in Fig 3 (mechanisms 1 and 3).

(4) *Increased urinary excretion of free and conjugated amines:* The increase in urinary excretion of tryptamine and tyramine occurring after administration of MAO inhibitors can be used as an indirect index of the degree of enzyme inhibition. More accurate, direct methods are now available for measuring MAO in biopsy material of peripheral tissues (Levine & Sjoerdsma 1963).

(5) *Nonspecific effects on other enzymes:* The hydrazines, in particular, inhibit diamine oxidase, dopa-decarboxylase and other enzymes (Pletscher *et al.* 1960). Iproniazid, pheniprazine and nialamide prolong the duration of hexobarbital hypnosis in mice (Laroche & Brodie 1960, Serrone & Fujimoto 1962). This effect is short-lasting, unrelated to the MAO inhibition, and is due to a decreased metabolism of hexobarbital in liver microsomes (Table 2). The imipramine-metabolite, desmethylimipramine, has also been shown to inhibit liver microsomal enzymes in rats (Sjöqvist & Gillette 1965). As Burns pointed out in this symposium (page 955), inhibitors of liver microsomal enzymes may, under certain circumstances, e.g. chronic administration to animals, speed up the metabolism of other compounds. The mechanism involved is not clear.

Table 2
Essential pharmacological properties of MAO inhibitors

(1) *Effects clearly related to MAO inhibition*
(*a*) Augmentation of central effects of monoamines and their precursors
(*b*) Potentiation and prolongation of the effects of sympathomimetic amines on blood pressure and smooth muscles
(*c*) Diminution and reversal of reserpine effects
(*d*) Experimental 'antidepressive' effect
(2) *Effects possibly related to MAO inhibition*
(*a*) Increase in motor activity
(*b*) Inhibition of intestinal motility
(*c*) Inhibition of ganglionic transmission
(*d*) Hypotensive effect (chronic administration)
(3) *Effects probably unrelated to MAO inhibition*
(*a*) Coronary dilatation
(*b*) Experimental liver damage
(*c*) Inhibition of conditioned reflexes
(4) *Effects unrelated to MAO inhibition*
(*a*) Immediate desynchronization of EEG
(*b*) Hypertensive effect (acute administration)
(*c*) Unspecific effects on liver microsomal / drug metabolism / and other enzymes

Modified from Pletscher *et al.* (1960)

It should also be emphasized that there are marked species differences in the effect of drugs on liver microsomal enzymes. It is, therefore, important to elucidate whether MAO inhibitors slow down drug metabolism also in man. It is possible that certain clinical interactions between MAO inhibitors and other drugs might be explained in this way. Thus, several drugs which are metabolized by liver microsomal enzymes, e.g. pethidine, pentobarbital and phenothiazines, evoke prolonged but essentially normal pharmacological effects in certain individuals treated with MAO inhibitors (Table 7). Pethidine may, in addition, be markedly potentiated immediately after parenteral injection in man. The rapid onset of this potentiation and its abnormal pharmacological character (for symptoms see Table 7) can hardly be explained in terms of a decelerated metabolism of pethidine. Furthermore, this reaction has been reported in a few patients treated with pargyline (Vigran 1964), and an immediate potentiation of pethidine occurs in rats pretreated with this drug (Sjöqvist 1965, unpublished), which is a rather specific MAO inhibitor compared to the hydrazines. Other mechanisms, such as release of brain amines, may very well be involved in this syndrome (cf. Table 7).

Pharmacological Properties of MAO inhibitors (Table 2)

Effects clearly related to MAO inhibition: Following injection of 5-hydroxytryptophan (5-HTP), 3, 4 dihydroxyphenyl alanine (DOPA), L-tryptophan, L-tyrosine, and L-phenylalanine,

which easily pass the blood-brain barrier, there is an increase in the brain levels of the corresponding amines, i.e. 5-HT, DA (NA), tryptamine, tyramine and beta-phenylethylamine. This increase is particularly pronounced in animals treated with MAO inhibitors. As a result, the central pharmacological effects of the amine precursors, e.g. arousal effect, hyperthermia, motor stimulation and tremor, will be enhanced in such animals (Carlsson *et al.* 1957, Udenfriend *et al.* 1957, Everett *et al.* 1959, Blaschko & Chrusciel 1960, Everett 1961, Shimizu *et al.* 1964).

Broad beans, containing DOPA, have been reported by Hodge *et al.* (1964) to cause hypertension in patients treated with pargyline (Table 4). The ethanol-soluble fraction of bean pod evoked hypertensive effect when injected intravenously to rats given pargyline previously. Pretreatment of rats with an inhibitor of DOPA decarboxylase (which inhibits the formation of dopamine) completely blocked this pressor response.

Central potentiation of DOPA (300 mg/day) has been described in patients treated with pargyline (100 mg/day) for psychotic depression (Everett *et al.* 1963). The effects consisted of increased motor responsiveness, restlessness, insomnia and anxiety, but the drug combination had no evident effect on mood. Kline *et al.* (1964) recently stated that DL-5-HTP might enhance the anti-depressive effects of MAO inhibitors. However, combination therapy with amine precursors and MAO inhibitors is potentially dangerous.

MAO inhibitors augment and prolong the pressor effects of dopamine and tyramine. They also enhance the action of dopamine and tyramine, but not of noradrenaline, on the contractile force of the heart (Furchgott *et al.* 1955, Helmer 1957). The increased activity of usually innocuous amounts of these amines, e.g. tyramine found in certain cheeses, may be manifested clinically by hypertensive crises (Tables 3 and 4).

Asatoor *et al.* (1963) demonstrated the presence of large quantities of tyramine in certain cheeses. These authors suggested that tyramine was responsible for the hypertensive episodes evoked by cheese in patients treated with MAO inhibitors (references in Table 4). This hypothesis has been confirmed pharmacologically in both animals (Blackwell & Marley 1964, Natoff 1964*a*, *b*, 1965) and man (Horwitz *et al.* 1964). According to these authors, most orally administered tyramine is metabolized immediately by intestinal and, to a lesser extent, hepatic MAO. Following inhibition of MAO, the absorption of the amine is increased severalfold, and it quickly enters the circulation, exerting an effect which simulates that of intravenous injection (cf. Natoff 1965). It may now cause prolonged release of noradrenaline and evoke pressor effects. Horwitz *et al.* (1964) found that 20 g of a certain Cheddar cheese is enough to induce marked hypertension in patients treated with pargyline (cf. Table 5). These authors could control and block the pressor effects with phentolamine (Rogitine), an alpha-adrenergic blocking drug. This is additional pharmacological proof of amine mediation of the pressor reaction.

Table 3
Interaction between MAO inhibitors and sympathomimetics

Specific agents	*Mechanism of potentiation*■	*Symptoms*	*Treatment*	*Comments*
Noradrenaline (other directly acting agents)	4 (Horwitz *et al.* 1960)	Potentiated adrenergic effects	Alpha-adrenergic blocking agent▲	
Dopamine (DA)	1+4 (Horwitz *et al.* 1960)	Hypertension		Experimental interest only
Tyramine (TA)	1+2 (Horwitz *et al.* 1964)	Hypertension	Alpha-adrenergic blocking agent▲	
Amphetamine●	2+9 (Zeck 1961)	Severe headache, hypertensive crisis, cardiac arrhythmias, chest pain, circulation insufficiency. For drugs passing the blood-brain barrier central excitation possible as well	Hypertensive crisis: alpha-adrenergic blocking agent. Cardiac symptoms: beta-adrenergic blocking agent. Central adrenergic symptoms: chlorpromazine	All fatal complications with tranylcypromine. Less dramatic cases reported also with phenelzine
Methamphetamine●	2+9 (Dally 1962, Mason 1962, Stark 1962, McDonald 1963)			
Dextroamphetamine				
Metaraminol				
Phenylephrine				
Ephedrine●	2+9 (Low-Beer & Tidmarsh 1963)			
Methylphenidate	2+9 (Sherman *et al.* 1964)			

Agents underlined have caused potentially dangerous interactions.
●Reported to have caused fatal interactions.
■Numbering of mechanisms of potentiation corresponds to Fig 3.
▲E.g. phentolamine (Horwitz *et al.* 1964).

Table 4
Interaction between MAO inhibitors and certain foods

Specific substance	*Mechanism of potentiation*■	*Symptoms*	*Treatment*	*Comments*
Cheese●	1+2 (Bethune *et al.* 1963, Blackwell 1963*a*, *b*, Beresford-Davies 1963, Womack 1963, Cuthill *et al.* 1964, Horwitz *et al.* 1964, Leonard *et al.* 1964)	Hypertensive crisis	Phentolamine	These foods contain different amines, predominantly tyramine (cf. Table 5)
Yeast products Beer? Wine?	(Blackwell *et al.* 1964)			
Broad beans (*Vicia faba* L.)	6+1 (Hodge *et al.* 1964)	Hypertension. Possibly central adrenergic symptoms	Phentolamine. Chlorpromazine	Contain DOPA
Coffee, Cola drinks	9 (Kline 1959)	Hyperexcitability	Not needed	Contain caffeine
Bananas?	1	?		Bananas contain serotonin (cf. Udenfriend *et al.* 1959)

See footnote to Table 3

The 'cheese reaction' may be evoked in patients treated with any MAO inhibitor. It has been reported after phenelzine, nialamide, pargyline and especially tranylcypromine. The reported incidence of vascular crises after tranylcypromine varies between 3% and 20% (Blackwell 1963*b*, Cooper *et al.* 1964, Lees & Burke 1963). Bethune *et al.* (1964) showed that the incidence of the syndrome dropped from 18% to 4% after the patients were warned not to eat cheese. The frequency of hypertensive crises after other MAO inhibitors is considerably lower, presumably because they have little or no amphetamine-like effects.

A yeast product, Marmite, has been reported to contain enough tyramine to cause pressor effects in animals treated with MAO inhibitors (Blackwell *et al.* 1964, cf. Table 5). Possibly other foodstuffs, e.g. certain fruits containing dopamine, tyramine, serotonin, &c., may cause bizarre effects in these patients (Udenfriend *et al.* 1959). The tyramine content of some foods has been determined by Horwitz *et al.* (1964) (Table 5).

Table 5
Tyramine content of various foods

Product	*Tyramine (μg/g or ml)*	*Amount (g or ml) containing at least 10 mg tyramine*▲
Cheeses:		
Camembert	86	110
Stilton	466	20
Brie	180	55
Emmenthaler	225	50
NY State Cheddar	1,416	7
Gruyère	516	20
Yeast	Not detectable	
Yoghurt	Not detectable	
Beer	1·8–4·4	
Wines:		
Chianti	25·4	400
Port	Not detectable	
Sherry	3·6	

After Horwitz *et al.* (1964)
▲10 mg of tyramine will in all probability evoke a marked pressor effect in patients with an inhibited MAO (cf. text)

Sympathomimetic amines act either directly, by combining with receptors, or indirectly, by causing the release of noradrenaline from nerve terminals (Burn & Rand 1958, Trendelenburg 1963). After MAO inhibition the latter amines (tyramine, amphetamine, ephedrine, &c.) may evoke enhanced effects, whether they are substrates of MAO or not (cf. Everett *et al.* 1963). MAO inhibitors may increase the noradrenaline stores in sympathetic nerve endings, and indirectly acting amines may now release larger amounts of the transmitter, which then reacts with receptor sites. This mechanism can operate peripherally as well as centrally (Fig 3). It may explain most of the clinical reports of marked potentiation of amphetamine, methamphetamine, ephedrine and methylphenidate in patients treated with MAO inhibitors (for references see Table 3). To judge from the clinical literature (Table 3), tranylcypromine and phenelzine have caused most of the cases of harmful interactions with sympathomimetics. This may be due to their amphetamine-like structure. In addition they are commonly used.

Pheniprazine, phenelzine, and particularly tranylcypromine exert amphetamine-like actions that are unrelated to their effect on MAO (Table 2:4 *a-c*). Thus, both pheniprazine and tranylcypromine cause initial pressor effects in dogs, which can be blocked by phentolamine and are probably due to the release of noradrenaline (Gillespie 1960, Spencer *et al.* 1960). These drugs may, therefore, act both as releasing agents and as MAO inhibitors. Interestingly, both tranylcypromine and phenelzine have been reported to

Table 6
Interaction between MAO inhibitors and antidepressant drugs

Specific drugs	*Mechanism of potentiation*■	*Symptoms*	*Treatment*	*Comments*
Imipramine●	8 Inhibit uptake of NA in adrenergic nerves (Singh 1960, Ayd 1961, Kane & Freeman 1963, Adams *et al.* 1963, Brachfeld *et al.* 1964)	Excitation, tremor, profuse sweating, hyperpyrexia, delirium, clonic and tonic convulsions, rigidity, coma.	Chlorpromazine (Grantham *et al.* 1964) Barbiturates contraindicated?	Reported after therapeutic doses of imipramine-like drugs
Amitryptyline	(Jarecki 1963)			
MAO inhibitors: All	5 Additive effects (Goldberg 1964)	Agitation, tremor, opisthotonus, coma, hyperpyrexia	Symptomatic. Caution with other drugs	
Those with amphetamine-like effects: Tranylcypromine●	5+3 (McClure 1962, Enoch 1963, Blackwell 1963 *a*, *b*, Lees & Burke 1963, Cooper *et al.* 1964, Schrire 1963)	Hypertensive crisis (mainly systolic hypertension). Clinical picture may resemble pheochromocytoma or subarachnoid bleeding. In rare instances, death because of intracerebral bleeding	Alpha-adrenergic blocking agent	At least 20 fatal cases reported in both England and the United States
Phenelzine	(Sarwer-Foner *et al.* 1959, Budow 1960, Gates 1963)	Similar, but less dramatic pictures described		No fatal complications reported

See footnote to Table 3

cause hypertensive crises without concomitant medication (Table 6). Furthermore, these MAO inhibitors evoke central stimulation by an immediate amphetamine-like action. This is manifested as an initial arousal effect in the EEG pattern (Costa *et al.* 1960). However, the persistent desynchronization of EEG caused by pheniprazine is correlated with the increase in brain monoamines (Costa *et al.* 1960, Shimizu *et al.* 1964).

Pretreatment of animals with MAO inhibitors counteracts many effects caused by reserpine and may even produce a reversal of the reserpine syndrome. In iproniazid-treated animals, reserpine induces excitation, hyperthermia, mydriasis and piloerection compared to sedation, hypothermia and miosis in the normal animal (Besendorf & Pletscher 1956, Brodie *et al.* 1956). Reserpine-released amines, which are normally metabolized by MAO, will now be present in high concentrations in the brain and will cause central stimulation. It is therefore not surprising that a paradoxical, exciting effect of reserpine has been observed in patients treated with MAO inhibitors (Voelkel 1959).

Spector *et al.* (1963) found a clear-cut relationship between the behavioral effects and the increase in brain noradrenaline after administration of pargyline to laboratory animals. Results obtained by depleting the amine stores with reserpine and, three hours later, blocking MAO, suggested that free noradrenaline is extremely active in antagonizing reserpine 'depression' in animals. These authors also discussed possible pitfalls in relating changes in behavior to the brain amines and MAO inhibition. Unfortunately, there are few adequate studies correlating actual inhibition of MAO with clinical changes in depressed patients treated with MAO inhibitors (Cole 1964).

Effects possibly related to MAO inhibition: Orthostatic hypotension develops gradually after prolonged administration of MAO inhibitors, and is the basis for the use of pargyline in the treatment of hypertension. There is considerable con-

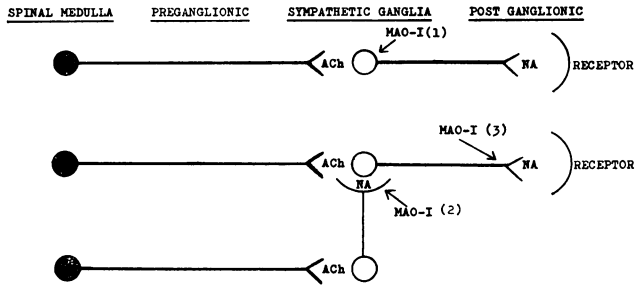

Fig 2 *Possible sites of action of MAO inhibitors (MAO–I) in the peripheral sympathetic system. Filled circles: preganglionic cholinergic neurons. ACh=acetylcholine. Open circles: postganglionic adrenergic cell bodies. NA=noradrenaline. Compare text and Norberg & Sjöqvist (1965)*

troversy regarding the site of the sympathetic block and its relation to MAO inhibition. As shown in Fig 2, MAO inhibitors depress ganglionic transmission presumably by acting directly on the sympathetic ganglion cells. This mechanism is unrelated to MAO inhibition (Gertner 1961, Goldberg & DaCosta 1960). MAO inhibitors may also enhance inhibition of ganglionic transmission by acting on adrenergic interneurons, which recently have been demonstrated in sympathetic ganglia (Hamberger *et al.* 1963, 1965). Finally, certain MAO inhibitors, such as pargyline, inhibit the release of noradrenaline at postganglionic nerve endings in animals (Gessa *et al.* 1963). Under experimental conditions, the sympathetic blockade, observed after chronic inhibition of MAO, may be the consequence of replacement of noradrenaline by a false, inactive neurotransmitter (Kopin *et al.* 1965).

Even in patients who have developed orthostatic hypotension after MAO inhibitors, hypertensive reactions to amines may still take place. Moreover, the response to amines, which are not metabolized by MAO, can now be augmented (cf. p 969), due to 'denervation' supersensitivity of adrenergic receptor sites to any directly acting amine.

Effects probably or entirely unrelated to MAO inhibition: These effects are summarized in Table 2 and those of particular relevance for the understanding of drug interaction with MAO inhibitors have already been discussed.

Summary of Mechanisms of Interaction between MAO Inhibitors and Other Substances

A number of possible interactions between MAO inhibitors and other agents have been derived from the basic pharmacodynamics presented in the previous sections. The principal mechanisms involved are summarized in Fig 3. The scheme is purposely arranged as a clock. If one starts at 1 p.m. and moves clockwise to 12 midnight, one will go from bright daylight to complete darkness as far as knowledge of mechanisms is concerned.

Clinical Aspects of Interaction between MAO Inhibitors and Other Substances

Tables 3–9 summarize the clinically important interactions between MAO inhibitors and different classes of drugs, e.g. sympathomimetics, antidepressants, CNS depressants, antihypertensives and other agents. Table 4 shows possible interaction between MAO inhibitors and certain foods. All agents underlined have been shown beyond doubt to evoke potentially dangerous effects in patients treated with MAO inhibitors. Drugs which have caused fatal complications in such patients are marked (see footnotes to Table 3). Mechanisms of 'potentiation' (used in its broader meaning to include true potentiation, prolongation and other types of interaction) are suggested for each individual agent and are described by figures corresponding to those used in Fig 3. Typical clinical symptoms are listed in the tables and details may be found in the corresponding references.

I wish to emphasize mechanisms of 'potentiation' rather than to describe the final result of the pharmacological events in terms of symptomatology. It is vital to understand the fundamental mechanisms involved in order to avoid these complications and to treat them properly when they occur. The tables will be commented upon briefly.

Interaction between MAO inhibitors and sympathomimetics: Data on these interactions are summarized in Tables 3–5. The most important complication of the simultaneous use of sympathomimetics and MAO inhibitors is the hypertensive crisis. The mechanism involved is now well understood (cf. p 972). Tranylcypromine an phenelzine can probably also cause hypertensive crises on their own. Tachyphylaxis rapidly develops to the initial pressor effects of these MAO inhibitors. This tachyphylaxis may be lost quickly when the administration of the drug is discontinued, while the MAO inhibition will persist for much longer (Ling 1962, Spencer *et al.* 1960). A similar mechanism may possibly be involved if patients take tranylcypromine and phenelzine irregularly. In this situation, pressor effects may reappear and even be enhanced because of the irreversible inhibition of MAO.

A great number of serious accidents have occurred after intravenous injection of therapeutic doses of amphetamines to patients treated with MAO inhibitors.

The case reports (Table 3) do not permit an analysis of the relationship between these untoward reactions and the doses employed of various sympathomimetics. It appears that a hypertensive crisis may occur in occasional patients after extremely small doses of sympathomimetics. Thus, Zeck (1961) reported a fatality after the combination of tranylcypromine and 5 mg amphetamine orally.

The hypertensive crisis following administration of sympathomimetic amines in patients treated with MAO inhibitors should ideally be treated with an alpha-adrenergic blocking agent, e.g. phentolamine by slow intravenous injection (5 mg). Cardiac arrhythmias, which are probably due to stimulation of beta-receptors, may be con-

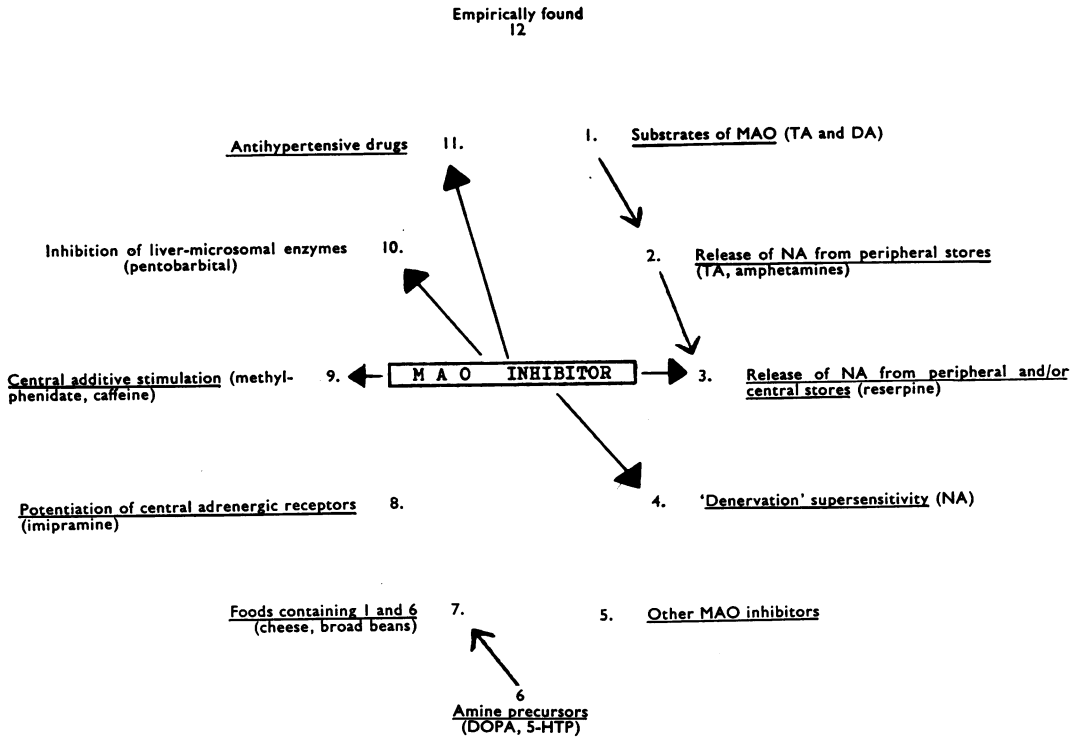

Fig 3 *Principal mechanisms involved in interactions between MAO inhibitors and other substances. Underlined mechanisms are reasonably predictable from animal experiments. For certain agents, several mechanisms may be involved (connected by arrows). Mechanisms 3, 4, 9, 10 and 11 (filled arrows) are dependent upon the pharmacological effects of the MAO inhibitor itself*

trolled by a beta-adrenergic blocking drug (Table 3). Symptomatic treatment of the hypertensive crisis without considering the mechanism involved is potentially dangerous. Such examples are treatment with ganglion-blocking drugs, reserpine and pethidine (Leonard *et al.* 1964, Mann & Laing 1963, Taylor 1962). The therapeutic value of ganglion-blocking drugs is not understandable unless an increased preganglionic sympathetic impulse flow contributes to the hypertensive crisis, but there is no experimental evidence to support this concept (cf. Fig 2). Reserpine and pethidine, given in high parenteral doses, are contraindicated in this situation as explained earlier.

Interaction between MAO inhibitors and foods: Data are summarized in Tables 4 and 5. The high incidence of headache in patients with the 'cheese reaction' may partly be caused by amines other than tyramine, such as histamine, present in certain cheeses. Histamine is a substrate of diamine oxidase, which is inhibited by certain hydrazines. Endogenous histamine and serotonin may possibly be potentiated by MAO inhibitors. These drugs may occasionally evoke bronchial asthma (Mathov 1963, Holmberg & Sjöqvist 1964*b*). Patients with carcinoid syndrome are known to flush after tyramine and certain cheeses (Levine & Sjoerdsma 1963, Waldenström *et al.* 1956), a reaction which might be enhanced after MAO inhibition. Patients with pheochromocytoma also show greatly enhanced pressor responses to intravenous tyramine (Horwitz *et al.* 1964). Accordingly, in patients developing hypertensive crises during therapy with a MAO inhibitor, one should consider the presence of a pheochromocytoma.

Interaction between MAO inhibitors and antidepressant drugs: Himwich (1961) studied the behavioral effects of single doses of tranylcypromine in dogs pretreated with imipramine (Tofranil) and found that tranylcypromine potentiated imipramine, probably independently of the MAO inhibition. The drugs evoked marked hyperpyrexia. This symptom has also been of major concern in patients who have reacted unfavorably to the combination of MAO inhibitors and iminodibenzyl derivatives.

However, most of these interactions may be explained in another way. Imipramine-like com-

Table 7
Interaction between MAO inhibitors and CNS depressants

Specific drugs	*Mechanism of potentiation*■	*Symptoms*	*Treatment*	*Comments*
Barbiturates	10 ? (cf. text) (Kline 1959, Domino *et al.* 1962)	Enhanced and prolonged sedation	Symptomatic	
Phenothiazines	As above and via brain amines? (Kline 1959, Goldberg 1964)	Increased extrapyramidal reactions. Hypertension		
Pethidine●	3+10 ? (Shee 1960, Palmer 1960, Reid & Jones 1962, Pells-Cocks & Passmore-Rowe 1962, Taylor 1962, Bradley & Francis 1963, Vigran 1964)	Excitation, rigidity and coma within mins. after the injection. Hypo- or hypertension, impaired respiration, hyperpyrexia, shock. Also prolonged pethidine effects	Depending upon clinical picture; chlorpromazine, nalorphine, prednisone, or metaraminol	The syndrome has been described after iproniazid, phenelzine and pargyline

See footnote to Table 3

pounds are known to inhibit the uptake of amines in monoaminergic nerve endings (Dengler *et al.* 1961) and to sensitize adrenergic and tryptaminergic receptors to the action of noradrenaline and serotonin (Sigg 1962, Sigg *et al.* 1963). MAO inhibitors increase the amount of these amines available extraneuronally to receptor sites (see p 969).

Everett *et al.* (1963) studied the observable central effects of imipramine in mice, pretreated with pargyline and DOPA. The central effects of DOPA were proportionally enhanced by increasing doses of imipramine.

Serious reactions and even fatalities have been reported with the combination of iminodibenzyl derivatives (imipramine, amitryptyline (Tryptizol), &c.) and MAO inhibitors, given in therapeutic doses. Symptoms have ranged from dizziness, nausea, vomiting, and excitation to coma, hyperpyrexia, convulsions and circulatory collapse (Table 6). Near fatal reaction has been reported after 'one tablet' of imipramine, given to a patient treated with tranylcypromine for a few days (Brachfeld *et al.* 1964) and a serious reaction occurred in a patient treated with phenelzine, who was given 25 mg of imipramine by intramuscular injection (Singh 1960). An alarming picture has also been described in a patient treated with imipramine for a few weeks and then given 15 mg of etryptamine (Kane & Freeman 1963). The latter finding is of interest in the light of Himwich's experiments (1961).

The observations by Everett *et al.* (1963) raise the question whether the clinical interactions between MAO inhibitors and imipramine-like compounds are dose-related. A few investigators feel that the dangerous interactions could be avoided by proper adjustment of dosage regimes (Sargant 1963, Everett 1965). The general feeling is that these two drug groups should not be used together. In fact, a drug-free interval of about two weeks (permitting recovery of MAO) is recommended when switching from a MAO inhibitor to an imipramine-like compound. Chlorpromazine, because of its central adrenolytic properties, might be the drug of choice in the treatment of imipramine-MAO-inhibitor incompatibility (cf. Grantham *et al.* 1964).

Since phenothiazines may have augmented effects in patients treated with MAO inhibitors (Kline 1959), the chlorpromazine dose should be carefully titrated according to the clinical response (Table 7). Recently, a fatality was reported in a patient given pargyline and methotrimeprazine, a phenothiazine derivative (Barsa & Saunders 1964). The picture was very similar to the interaction seen between imipramine-like drugs and MAO inhibitors. This further illustrates the difficulty of analyzing these case reports in terms of mechanisms of interaction.

Table 8
Interaction between MAO inhibitors and antihypertensive drugs

Specific drugs	*Mechanism of potentiation*■	*Symptoms*	*Comments*
Thiazide diuretics	Probably additive effect (Goldberg 1964)	Hypotension	
Methyldopa	3+6 (van Rossum 1963, Natarajan 1964)	Hypertensive reaction and central excitation possible	Central excitation not yet reported in man
Reserpine and related compounds	3 (Voelkel 1959, Gradwell 1960)	Reversal of the reserpine syndrome: marked hyperexcitation	High dose of reserpine necessary. Rarely seen in man. Hypertensive crisis after MAO inhibitors, should not be treated with reserpine

See footnote to Table 3

Interaction between MAO inhibitors and other drugs: These interactions are summarized in Tables 8 and 9. For the drugs mentioned in Table 9, mechanisms of interaction are unknown. The overall data strongly indicate that when other drugs must be used in patients treated with MAO inhibitors, the doses should be reduced considerably. A normal therapeutic dose of many drugs has to be considered as an overdose in these patients.

Table 9
Interaction between MAO inhibitors and other drugs found empirically

Specific agents	*Mechanism of potentiation* ■	*Symptoms*	*Comments*
Anesthetics	12 Not clear (Goldberg 1964)	Enhanced CNS depression	Poor documentation
Chloral hydrate	12 Not clear (Howarth 1961)	Enhanced CNS depression	Poor documentation
Anti-Parkinson drugs	12 Not clear (Shaw 1964)	Potentiation	Poor documentation
Insulin	12 Not clear (Cooper & Keddie 1964)	Hypoglycemic reactions	Reported for mebanazine
Cocaine	12+8 (Clementz & Benazon 1962)	Hyperexcitation	Uncertain association

See footnote to Table 3

Concluding Remarks

This survey on the mechanisms of interaction between MAO inhibitors and other drugs, briefly condensed in Fig 3, demonstrates how complicated pharmacotherapy has become during recent years. It is essential that physicians think in terms of mechanism of action when using potent drugs like MAO inhibitors. This approach could reduce the number of dangerous complications which still occur after uncautious use of these drugs, particularly in combination with other agents. Doctors using MAO inhibitors ought to know key concepts about the biochemical pharmacology of adrenergic neurons. This is especially true since most of the hazardous interactions reported between MAO inhibitors and other drugs are predictable from animal experiments.

The introduction into medical practice of potent drugs such as MAO inhibitors necessitates a firmer association between basic pharmacology and clinical medicine. This could be established by the development of departments in clinical pharmacology at university centers. A largely increased teaching and research program devoted to mechanisms of action of drugs in man is an excellent method to safeguard pharmacotherapy, far superior to the other alternative, the withdrawal of useful drugs from the market.

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Drug Interaction in the Field of Analgesic Drugs

by Louis Lasagna MD
(Departments of Medicine and of Pharmacology and Experimental Therapeutics, Johns Hopkins Hospital, Baltimore, Maryland, USA)

Abstract
The evidence for believing that mixtures of aspirin, phenacetin, and caffeine provide advantages over the individual components of these mixtures is reviewed, and doubt expressed as to the rationale for the use of these mixtures in ordinary medical practice. The syndrome of 'analgesic nephropathy' is also reviewed, and on the basis of experiments in healthy volunteers it is suggested that individual ingredients of analgesic mixtures be scrutinized more carefully in an attempt to track down the agents responsible for toxic effects.

The use of phenothiazine compounds, alone or in mixture with narcotics, is reviewed, and the opinion expressed that methotrimeprazine has special analgesic attributes.

The narcotic antagonists represent an extremely interesting group of drugs which possess analgesic activity as well as the ability to antagonize certain effects of morphine and other narcotic agents. The patterns of respiratory effect, psychotomimesis, and abstinence phenomena seen with these antagonists illustrate the possibility of dissociating certain effects usually assumed to be linked inseparably in drugs possessing the analgesic power of morphine.

This discussion will be limited to three major areas: (1) Certain analgesics commonly taken by mouth. (2) Phenothiazine tranquilizers as analgesic agents. (3) Narcotic antagonists and 'narcotic antagonist-analgesics'.

Drugs of the aspirin-phenacetin[1]-caffeine (APC) class are widely used by the lay public and often prescribed by physicians. One might well ask: Why are these mixtures so popular? Why were they first proposed? If the introduction of APC mixtures can be attributed to a rational approach at either the animal or clinical level, the historical evidence has escaped me. It is more likely (Smith 1958) that the APC tablet was a result of the polypharmacy so prevalent in the last century. Phenacetin (acetophenetidin) seems to have been introduced, like aspirin, as an antipyretic drug, and perhaps as a euphoriant, rather than as an analgesic. With the passage of time, reports began to appear of its use as an analgesic, particularly in cases of headache, migraine, and neuralgia. The use of caffeine as a stimulant is well known and pharmacologically acceptable, but its use in the management of headaches is in a large part based on anecdotal reports, rather than on modern scientific trials.

[1]acetophenetidin in USA